

REMARKS/ARGUMENTS

Upon entry of the current amendment, claims 31, 33, 35-40, and 42-57 are pending in the present application, with claims 31, 35-36, 39-40 and 42-46 being amended, new claims 50-57 being added, and claim 41 being canceled hereby.

With reference to paragraphs of the published application, support for the amendment to claim 31 can be found in, *e.g.*, paragraph 265, which discusses administration of test agents to multiple teleosts, in, *e.g.*, paragraphs 292-294, which discusses responses indicative of a pharmacological activity, including a therapeutic activity, and the use of positive and/or negative controls to assess such activity, and in, *e.g.*, paragraph 108, which discusses combining the different screening methods described in the application for detecting various activities of a test agent. Claim 35 is amended to reflect the amendments made to claim 31. Support for the amendment to claim 36 can be found, *e.g.*, in paragraph 287. Support for the amendments to claims 39 and 40 can be found, *e.g.*, in paragraphs 265 and 287. Support for the amendment to claim 42 can be found in, *e.g.*, paragraphs 250, 252, 258 and 290, and support for the amendments to claims 43-46 can be found in, *e.g.*, paragraphs 256-257. Support for new claim 50 can be found in, *e.g.*, paragraphs 250 and 294, support for new claims 51-52 can be found in, *e.g.*, paragraph 289, and support for new claims 53-54 can be found in, *e.g.*, paragraphs 251 and 288. Support for new claim 55 can be found in, *e.g.*, paragraph 265. Support for new claims 56-57 can be found in, *e.g.*, paragraph 78. No amendment should be construed as acquiescence in any ground of rejection.

Each of the Examiner's comments are addressed in the order made. References to paragraph numbers made below refer to the published application, unless otherwise indicated.

1. Priority

The Examiner indicates that applicants' priority claim was denied in the Office Action of August 3, 2006. *See* p. 2 of the OA. Applicants reiterate that the issue of priority does not currently appear to be material to the grounds of rejection raised by the Examiner, but reserve the right to address the issue if it becomes relevant in future proceedings.

2. §112, First Paragraph Rejection

The Examiner has rejected claims 31, 33, and 35-38 pursuant to 35 USC 112, first paragraph because the specification allegedly does not reasonably provide enablement for screening an agent for a therapeutic activity. *See* p. 3 of the OA. The Examiner asserts that the specification does not support concomitant screening of an agent for a therapeutic activity and a toxic activity, but rather screening for toxic effects of agents known to have a therapeutic effect. *See* p. 4 of the OA. The Examiner further asserts that the specification does not provide adequate guidance for a person of skill to perform a screen for a therapeutic activity, nor to identify what constitutes a therapeutic activity. *See* pp. 4-5 of the OA. Applicants disagree with the Examiner's conclusion, but have amended independent claim 31 to recite administration of the agent to a plurality of teleosts and detection of toxic activity and therapeutic activity in different teleosts.

A. The specification clearly contemplates a screening method combining an assay for a toxic activity with an assay for a therapeutic activity

The Examiner asserts that the specification supports only a screen for toxic effects of agents *known* to have a therapeutic effect. *See* p. 4 of the OA. Applicants direct the Examiner's attention to, *e.g.*, paragraph 212 (which corresponds to p. 65, lines 7-21 of the filed application referred to by the Examiner). Paragraph 212 provides that "combined methods are useful in assessing multiple effects of an agent, including desired and undesired responses ... [and that] the ability to assess multiple activities and responses in an animal due to the administration of an agent is of particular benefit in *identifying* potential therapeutic compounds and assessing their side effects" (emphasis added). This passage makes clear that the combined screening methods described in the application include *identifying* potential therapeutic compounds, rather than merely assessing the toxicity of compounds known to have a therapeutic effect. At least in some cases, a toxic activity of an agent will be a side effect of an otherwise therapeutic compound. Thus, the specification supports a screening method for detecting both a therapeutic activity and a toxic activity.

The Examiner further asserts that the specification does not support the concomitant screening of an agent for therapeutic and toxic effects. *See* p. 4 of the OA. As mentioned above, applicants have amended independent claim 31 to address the Examiner's concern regarding screening for a toxic activity and a therapeutic activity in the same teleost. Applicants direct the Examiner's attention to, *e.g.*, paragraph 259, which provides that methods for screening agents for toxic activity can be combined with other methods of the present invention, "including" methods of screening agents for angiogenesis activity and cell death activity. Angiogenesis activity and cell death activity are each described as therapeutic activities within the specification. *See, e.g.*, paragraph 16, which provides that "[i]n some methods, the pharmacological activity [which includes therapeutic activity, *see* paragraph 292] is modulation of angiogenesis ... or modulation of apoptosis." Moreover, use of the term "including" in paragraph 259 with reference to combining methods of screening for toxic activity with other methods of the invention is not limiting, and clearly contemplates the inclusion of other methods of the invention, such as methods of screening an agent for a therapeutic activity (*see* paragraph 15, and recall that "pharmacological activity" encompasses "therapeutic activity") Paragraph 260 provides that a variety of techniques can be used to separately analyze multiple activities and responses in the teleost. Thus, the specification clearly supports a method directed to screening an agent for both a toxic activity and a therapeutic activity as presently claimed.

B. The specification defines a therapeutic activity and provides adequate guidance for a person of skill to perform a screen for a therapeutic activity

The Examiner asserts that in order to screen for a therapeutic activity, a disease state to be remedied or an effect of the agent to be screened must be known, and that the specification does not teach what activity is a "desired activity" or how to screen for such an activity. *See* p. 4 of the OA.

Applicants do not claim a "desired activity," but rather a therapeutic activity, which the specification defines as "any activity of ... an agent ... which diminishes or eliminates pathological signs or symptoms when administered to a subject exhibiting the pathology." *See* paragraph 68. Thus, the meaning of "therapeutic activity" is clearly defined by the specification.

Moreover, although no specific disease state or effect is identified in the definition of "therapeutic activity" referred to above, the claimed method is directed to a generally applicable screening assay for evaluating an agent for both a toxic activity and a therapeutic activity. Therefore, it is not necessary to recite a specific disease state or effect of the agent on the disease itself. Rather, a response that is indicative of a therapeutic activity, defined by controls selected by an investigator with regard to the desired therapeutic activity of interest, can be identified by the skilled practitioner. In this respect, applicants have amended claim 31 to recite a step of detecting a change in a response indicative of a therapeutic activity in the teleost relative to a control teleost.

The specification includes a general description of what a response, "indicative of pharmacological activity" (which includes therapeutic activity as indicated above) can include. *See* paragraph 292. For example, responses indicative of a pharmacological activity can include increases or decreases in the number of cells or the concentration of a cellular marker, such as an enzyme or a secondary metabolite. Such responses can also include modulation of a cellular pathway, or the promotion or inhibition of a physiological event such as cell growth or differentiation. *Id.* These responses can be detected by, for example, detecting the presence or quantity of particular nucleic acids or proteins. *Id.* As described above, a response indicative of a therapeutic activity, as claimed, need not be the therapeutic activity itself, but rather a change in a response as compared to a control that indicates to an investigator that the agent is likely to exhibit the desired therapeutic activity when administered to a subject exhibiting the associated pathology. The skilled investigator can readily determine the appropriate response indicative of a desired therapeutic activity to suit his or her needs. Thus, the specification provides adequate guidance for one of skill to perform the claimed screening method to assess an agent's therapeutic activity.

In addition, the Examiner asserts that the specification does not provide any guidance with respect to what characteristics would define an agent as therapeutic when administered to a normal, wildtype, or otherwise healthy teleost. *See* p. 5 of the OA. Applicants submit that whether a particular response indicative of a therapeutic activity, as discussed above, is detectable in a wildtype or otherwise normal teleost can be ascertained by an investigator

using a positive control, as discussed in the specification at, *e.g.*, paragraph 294. In any event, applicants note that claim 31 recites no limitation characterizing the teleost as wildtype or otherwise indicating whether the teleost is affected by a disease. Thus, the specification enables one of skill to perform the claimed screening method to assess an agent's therapeutic activity.

Claims 33, and 35-38 depend directly or indirectly from claim 31 and are enabled for the same reasons described above, as are new claims 54 and 56. Based on the foregoing, applicants respectfully request withdrawal of this ground of rejection.

3. §112, Second Paragraph Rejection

The Examiner has rejected claims 31, 33, and 35-40 pursuant to 35 USC 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that "[t]o promote a therapeutic activity is not commensurate in scope with having a therapeutic activity." *See* p. 6 of the OA.

Applicants have amended independent claim 31 to delete "assessing whether the agent is effective to promote the therapeutic activity," and submit that the amended claim language adequately addresses the Examiner's rejection. The rejection of the dependent claims is also addressed by the amendment to claim 31.

Based on the foregoing, applicants respectfully request withdrawal of this ground of rejection.

4. §102(b) Rejection

The Examiner has rejected claims 42-46 pursuant to 35 USC 102(b) as allegedly being anticipated by Mizell *et al.*, *Int. J. Dev. Biol.* **41**:411-423 (1997). The Examiner asserts that Mizell teaches a method for screening an agent for a toxic activity in a teleost by administering an agent to multiple embryos and detecting toxic effects by monitoring CYP1A activity. *See* p. 7 of the OA.

Applicants have amended independent claim 42 to recite addition of the test agent to culture media containing a teleost. Mizell does not discuss adding an agent to culture medium containing a teleost, as claimed, and thus does not anticipate amended claim 42. Mizell

discusses microinjection of both zebrafish and medaka, as well as contacting dechorionated zebrafish with a droplet of "various chemical pollutants" in a 10 cm Petri dish. In the latter method, a 250 µl droplet of a solution comprising one or a combination of test agents is placed in a Petri dish and a single embryo is placed in the droplet. After a 30 minute period of exposure, the embryo is removed from the droplet, rinsed three times in embryo rearing solution (ERS), and transferred to a Petri dish half-filled with ERS. *See* p. 421 of Mizell. There is no discussion that indicates that the test agents are added to the culture medium containing the teleost. Rather, the embryo is placed into the droplet comprising the test agent and thereafter washed and placed in culture media.

Claims 43-46 depend directly or indirectly from claim 42 and are novel for the same reasons described above with reference to independent claim 42, as are new claims 50-53, 55 and 57. Based on the foregoing, applicants respectfully request withdrawal of this ground of rejection.

5. §103(a) Rejections

The Examiner has rejected claim 41 pursuant to 35 USC 103(a) as allegedly being unpatentable over Mizell (*supra*) in view of Maccabbin *et al*, *Aquatic Toxicology* 9:277-286 (1986), or Black, *Aquatic Toxicology* 11:129-142 (1988), or Marty *et al.*, *Aquatic Toxicology* 17:45-62 (1990). *See* p. 7 of the OA.

Applicants have canceled claim 41 and the rejection is therefore moot.

The Examiner has also rejected claims 47-48 pursuant to 35 USC 103(a) as allegedly being unpatentable over Mizell in view of Terse *et al.*, *Toxicon* 31:913-919 (1993). *See* p. 9 of the OA. The Examiner asserts that Mizell teaches placing an embryo into a single droplet of medium in a single large Petri dish, but does not teach placing an embryo in a multi-well plate, or in a volume of 300 µl or smaller, as claimed. The Examiner further asserts that Terse teaches screening for toxic activity of various agents using a 96-well plate, and that standard 96-well plates have a volume of 300 µl or less per well. Finally, the Examiner asserts that one of skill would have been motivated to combine the references because a multi-well plate provides a convenient means of separating samples, and that one would have had a reasonable

expectation of success because the use of 96-well plates was standard in the art, and such plates serve the same purpose as the Petri dish used in Mizell. *See* pp. 9-10 of OA. Based on these assertions, the Examiner concludes that it would have been obvious to combine the teachings of the two references to arrive at the claimed invention. *Id.*

Claims 47 and 48 depend directly or indirectly from independent claim 42, which recites adding the test agent to culture media containing the teleost. Terse reports *in vitro* assays of murine and bovine cell cultures in multi-well plates. Neither Terse, nor any other reference cited by the Examiner discusses addition of a test agent to culture media containing a teleost, as presently claimed. As noted by the Examiner, Mizell discusses placing an embryo into a droplet of medium containing the test agent(s). *See* p. 9 of the OA, and p. 421 of Mizell. After exposure, the embryo is removed from the droplet, rinsed three times in embryo rearing solution (ERS), and transferred to a Petri dish half-filled with ERS. *See* p. 421 of Mizell. Similarly, Maccabbin reports placing a 1 μ l droplet of DMSO/agent solution directly on the surface of a teleost egg. *See* p. 279 of Maccabbin. In the Maccabbin method, the eggs are contacted with the DMSO droplet while lying on a gauze pad in a Petri dish, and then, following an exposure period to ensure absorption of the solution, removed and placed in aerated spring water. *See* p. 280 of Maccabbin. Black discusses the method of Maccabbin as useful for overcoming difficulties in achieving adequate exposure to chemicals via a noninvasive technique. *See* p. 137-138 of Black. Black also reports that sensitivity of trout embryos to chemical carcinogens was originally demonstrated by immersing eyed-stage ova in an aqueous solution of aflatoxin B₁. *See* p. 130 of Black, first full paragraph. Marty reports exposure of Medaka eggs to various chemical solutions by randomly distributing the eggs into solutions comprising the agents, followed by repeated rinsing of the eggs in embryo rearing medium (ERM) and placement in ERM. *See* p. 47 of Marty.

Clearly, none of the references cited by the Examiner discusses a method in which the test agent is added to culture media containing a teleost, as claimed by applicants. Rather, in each case, the reference discusses a method in which the teleost is immersed in a solution of the agent or contacted by applying a drop of the solution to its surface. Thus, no reference of record teaches this element of the claimed invention, and no motivation exists to modify the references

Appl. No. 10/678,765
Amdt. dated July 30, 2008
Reply to Office Action of February 8, 2008.

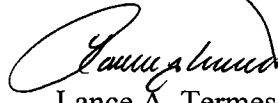
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to arrive at the claimed invention. Because claims 47 and 48 depend directly or indirectly from claim 42, neither would have been obvious for the reasons set forth above.

Based on the foregoing, applicants respectfully request withdrawal of this ground of rejection.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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